REPLACEMENT OF NUCLEAR ALKOXYL GROUPS BY THE ACTION OF GRIGNARD REAGENTS

BY

VAN RUSSELL GAERTNER

B. S., Bradley University, 1945

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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Introduction

The replacement of methoxyl groups *ortho* to hindered carbonyl groups by the action of Grignard reagents is a well-established reaction (1). The similarity between this process and the production of 2-ethyl-3-methoxybenzonitrile from 2,3-dimethoxybenzonitrile by the action of ethylmagnesium bromide, described by Richtzenhain (2), is at once evident. Chadwick (3), in attempting to extend this reaction, examined a series of methoxyaronitriles structurally similar to 2,3-dimethoxybenzonitrile but not possessing the 2,3-dimethoxy grouping. However, his work failed to uncover new examples of the replacement of methoxyl groups. It should be mentioned that recorded attempts to replace methoxyl groups *para* to hindered carbonyl groups have been unsuccessful (4,5).

This investigation was undertaken with the hope of finding other examples of the replacement reaction. It was anticipated that the vicinal dimethoxyl structure was a necessary and sufficient condition for the success of the replacement of alkoxyl groups by the radical of a Grignard reagent.

Discussion of Results

2-Methoxy-4-methylphenol was converted by means of the modified Duff procedure to 2-hydroxy-3-methoxy-5-methylbenzaldehyde, which was methylated and converted to the oxime; the latter was dehydrated to 2,3-dimethoxy-5-methylbenzonitrile by the action of acetic anhydride. This nitrile reacted with ethylmagnesium bromide in a ratio of 1:1.25 to give predominately 2-ethyl-3-methoxy-5-methylbenzonitrile. 2,3-Dimethoxybenzonitrile reacted with bromine in carbon

tetrachloride as a solvent to give 2,3-dimethoxybromobenzonitrile, which yielded both 2-ethyl-3-methoxybromobenzonitrile and 2-ethyl-3-methoxybromophenyl ethyl ketimine on treatment with ethylmagnesium bromide, indicating that simultaneous 1,2- *and* 1,4-addition had occurred. The position of the bromine atom in these compounds has not been established, but it was shown not to be in the 5 position since the oxime of the known 2,3-dimethoxy-5-bromobenzaldehyde was dehydrated to 2,3-dimethoxy - 5 - bromobenzonitrile, which proved to be different from the original product of bromination.

The previous observations that 2,3-dimethoxybenzonitrile undergoes replacement of the methoxyl group in the 2 position by the action of the ethyl and isopropyl Grignard reagents were confirmed, but *t*-butylmagnesium chloride gave exclusively the imine resulting from normal 1,2-addition.

A number of related nitriles was also investigated. 2,3-Ethylenedioxybenzonitrile was prepared from 2,3-dihydroxybenzoic acid through 2,3-ethylenedioxybenzoic acid, obtained by reaction with ethylene bromide and potassium hydroxide; the acid was converted to the chloride, then to the amide, and finally to the nitrile by dehydration with thionyl chloride. 2,3-Ethylenedioxybenzonitrile, as well as 2,3-methylenedioxybenzonitrile, veratronitrile, and piperonitrile, yielded only the imines resulting from the usual 1,2-addition. A mechanism involving 1,4-addition has been advanced to explain the replacement reaction.

These results led to the expectation that it might now be possible to replace a methoxyl group *para* to a hindered carbonyl group by taking advantage of the promoting effect of a flanking methoxyl group. This reaction has been realized. 3,4-Dimethoxybenzoylmesitylene, when treated with benzylmagnesium chloride, was converted to 3-methoxy-4-benzylbenzoylmesitylene. The structure of the product was proved beyond all reasonable doubt by its synthesis from *m*-methoxybenzoylmesitylene by the 1,6-addition of the benzyl

Grignard reagent. Similar results were obtained using the durene analogs. Ethyl and *t*-butyl Grignard reagents did not replace the *para* methoxyl group in 3,4-dimethoxybenzoylmesitylene, but evidence indicating that the reaction was successful with phenylmagnesium bromide was obtained. Benzylmagnesium chloride reacted with 3,4,5-trimethoxybenzoyldurene to replace the group in the 4 position, the product also being obtained from 3,5-dimethoxybenzoyldurene by the action of the same reagent. Piperonyldurene did not undergo replacement of the alkoxyl group when subjected to reaction with the benzyl Grignard reagent. This reagent replaced the *ortho* methoxyl group in 2,3-dimethoxybenzoylmesitylene, although ethylmagnesium bromide did not. It was concluded that a flanking methoxyl group is necessary to the replacement of a *para* methoxyl group in hindered diaryl ketones.

The ketones used in this investigation were obtained by reaction of the appropriate acid chlorides either with mesitylene or durene in the Friedel-Crafts reaction or with the corresponding Grignard reagents.

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VITA

The author was born in Centralia, Illinois, on July 4, 1924. He attended the public schools of Peoria, Illinois, and was graduated in chemistry from Bradley University in that city in 1945. In the same year he entered the University of Illinois as a teaching assistant in inorganic chemistry. He was a University fellow from June, 1947, until June, 1948.

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